analysis) of many complex molecular systems by computers. Typical molecular modeling applications have included enzyme-ligand docking, molecular diffusion, reaction pathways, phase transitions, and protein folding studies. Researchers in the biological sciences and the pharmaceutical, polymer, and chemical industries are beginning to use these techniques to understand the nature of chemical processes in complex molecules and to design new drugs and materials accordingly. Naturally, the acceptance of these tools is based on several factors, including the accuracy of the results in representing reality, the size and complexity of the molecular systems that can be modeled, and the speed by which the solutions are obtained. Accuracy of many computations has been compared to experiment and generally found to be adequate within specified bounds. However, the use of these tools in the prior art has required enormous computing power to model molecules or molecular systems of even modest size to obtain molecular time histories of sufficient length to be useful.

A1 Cont'd

Please replace the paragraph beginning at page 5, line 20 with the following rewritten paragraph:

A2

Some molecular dynamicists have experimented with implicit methods and rejected them as impractical. See, for example, Schlick, *Computational Molecular Dynamics: Challenges, Methods, Ideas*, Deuflhard *et al.* (ed.), Springer, 1999, p. 238. In particular, the propensity of stable methods to remove energy from a simulation through induced damping was considered a fatal flaw, as has been the large amount of computing time required by the nonlinear system at each timestep. See Schlick, *op. cit.*, pp. 238-9, and 244. The damping effect was considered a critical flaw because most molecular dynamics simulations are required to conserve energy. In Schlick's review cited above, the molecular models included Langevin terms that introduced artificial forces to restore the energy lost due to explicit damping and due to the stable integration method. These forces actually prevent the stable method from taking the large timesteps, as desired. Although implicit methods can be used effectively in such computations, there are also

many molecular modeling computations which do not need to conserve energy and our methods are particularly effective for those problems. We will teach how to employ implicit methods effectively in practical computations through judicious modeling choices and careful implementation.

A2

Please replace the paragraph beginning at page 8, line 24 with the following rewritten paragraph:

A3

With the translated physical parameters from the biochem components module 52, the physical model module 54 defines the molecular system mathematically. At the core of the module 54 is a multibody system submodule 66. The physical model module 54 and multibody system submodule 66 are described below in detail. Co-pending applications, U.S. Patent Appln. No. 10/053,348, entitled "METHOD FOR ANALYTICAL JACOBIAN COMPUTATION IN MOLECULAR MODELING," and U.S. Appln. No. 10/053,354, entitled "METHOD FOR RESIDUAL FORM IN MOLECULAR MODELING," both filed of even date and which claim priority from the previously cited provisional patent applications, are assigned to the present assignee and are incorporated by reference herein have further descriptions of the physical model module 54 and multibody submodule 66 from the perspective of the inventions disclosed in those patent applications.

Please replace the paragraph beginning at page 9, line 10 with the following rewritten paragraph:

A4

The visualization module 58 receives input information from the biochemical components module 52 and the analysis module 56 to provide the user with a three-dimensional graphical representation of the molecular system and the solutions obtained for the molecular system. Many visualization modules are presently available,

A4 cont'd

an example being VMD (A. Dalke, *et al.*, VMD User's Guide, Version 1.5, June 2000, Theoretical Biophysics Group, University of Illinois, Urbana, Illinois).

Please replace the paragraph beginning at page 9, line 23 with the following rewritten paragraph:

A5

The MBS is an abstraction of the atoms and effectively rigid bonds that make up the molecular system being modeled and is selected to simplify the actual physical system, the molecule in its environment, without losing the features important to the problem being addressed by the simulation. With respect to the general system architecture illustrated in Fig. 1, the MBS does not include the electrostatic charge or other energetic interactions between atoms nor the model of the solvent in which the molecules are immersed. The force fields are modeled in the submodule 62 and the solvent in the submodule 64 in the biochemical components module 52.

Please replace the paragraph beginning at page 10, line 30 with the following rewritten paragraph:

A6 sub B1

An asterisk indicates the transpose: $H^*(k)$, for example. A tilde over a vector indicates a 3 by 3 skew-symmetric cross product matrix: $\tilde{v}w \quad v \times w$. $\underline{\underline{E}}_i$ is an i by i identity matrix, and $\underline{0}_i$ is a zero vector of length i and $\underline{\underline{0}}_i$ is an i by i zero matrix.

Please replace the paragraph beginning at page 17, line 2 with the following rewritten paragraph:

A7

The dynamics residual, $\rho_u(k)$, appears because the Residual Form (in contrast to the Direct Form) of the equations of motion is used for the model. A detailed

description of the Residual Form and Direct Form of differential equations and their integration is found in the above-referenced co-pending U.S. Patent Appln. No. 10/053,354, entitled "METHOD FOR RESIDUAL FORM IN MOLECULAR MODELING," filed of even date.

A7

Please replace the paragraph beginning at page 19, line 21 with the following rewritten paragraph:

A8

The present invention is directed toward the molecular modeling of systems in which undamped high frequencies (and hence accurate solutions at very small time scales) are of no interest and which do not affect the long time-scale solution of the modeling of the molecular system. An example of the problem of so-called "stiff" systems might be the modeling of a simple pendulum that rocks back and forth with a period of one second. Now, a very small mass is attached to the end of the pendulum using a very stiff spring. The natural vibration of the small mass and spring system is, say 1000 cycles per second. That is, for each swing of the pendulum, the small mass vibrates 1000 times. Furthermore, the high frequency vibrations of the small mass are hardly noticeable because of their small amplitude, and don't affect the large scale swinging motion in any significant way for the behavior we are studying. An explicit integration method with timestep and error control is applied to solve the model of the swinging pendulum. If the integrator takes very tiny timesteps, even if the high frequency vibrations are much smaller than the error tolerance, then the system is "stiff".

Please replace the paragraph beginning at page 23, line 18 with the following rewritten paragraph:

A8 SUB B2

The implicit Euler integration method is illustrated in the flow chart of Fig. 6 for the vector function $\dot{y} = f(y,t)$ (where $y = (q,u)$, q representing the position states and u the velocity states of the molecular system). The function f includes both

the multibody system dynamics and the forces such as electrostatic attraction and repulsion, van der Waal's forces, and solvation forces. After an entry step 79, the first operation step 80 updates the Iteration matrix G. For all implicit integration methods, the Iteration matrix G has the form $G = I - \alpha J$, where I is the identity matrix, α is some scalar function of the timestep h_n, the timestep between time t_n and t_{n-1}, and J, the Jacobian given by $J \quad \frac{\partial f}{\partial y}$. For the implicit Euler method, $\alpha = h_n$. In passing, for additional savings in computer time, it should be noted that a very efficient method of computing Jacobian matrices from the residual form of equations is covered in previously cited co-pending U.S. Patent Appln. No. 10/053,348, entitled "METHOD FOR ANALYTICAL JACOBIAN COMPUTATION IN MOLECULAR MODELING," filed of even date and is assigned to the present assignee. As in the case of the present invention, the same referenced patent application also describes the use of internal coordinates to describe the state of the molecular system. For example, the rotation of one part of the molecule is described with respect to another part, rather than with respect to an external referenced coordinates. This further increases computing efficiency.

A8

Please replace the paragraph beginning at page 28, line 29 with the following rewritten paragraph:

A9

The present invention could be used to simulate many other biomolecules such as RNA, DNA, polysaccharides, and lipids. Also, molecular structures of combinations of these biomolecules such as protein-RNA complexes such as ribosomes and protein-DNA complexes such as histones and DNA in chromatin could be simulated. Processes which modify the structure of proteins could be simulated, such as the post translational modifications of proteins by chaperone proteins.